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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,632	HABERMANN, PAUL	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 7-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/01/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-20 are pending in the application.

[2] Applicants' amendment to the claims, filed November 01, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicants' amendment to the title of the specification, filed November 01, 2004, is acknowledged.

[4] Receipt of an information disclosure statement (IDS), filed November 01, 2004, is acknowledged.

[5] Claims 3-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

[6] Claims 1-2 and 7-20 are being examined on the merits.

[7] Applicant's arguments filed November 01, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[8] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

[9] The reference cited in the IDS filed November 01, 2004 has been considered by the examiner. It is noted the cited US non-provisional patent application has been published as US Patent Application 2002/0173620 A1. Applicants state the IDS also cites WO 02/04486 and DE 34 30 556, however, these references have not been cited on the IDS filed November 01, 2004.

Specification/Informalities

[10] The objection to the specification for the use of trademarks as stated in item [8] of the Office action mailed May 20, 2004 is maintained for the reasons of record. Applicants note the examiner's admonition, but have failed to amend the specification. It is suggested that applicants capitalize trademarks wherever they appear and accompany them with the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112, Second Paragraph

[11] The rejection of claim 17 under 35 U.S.C. 112, second paragraph, as set forth at item [9], part [c] of the Office action mailed May 20, 2004 is maintained for the reasons of record and the reasons stated below. Applicants assert the recitation of "removing the protein encoded by protein(Y) from the fusion protein" does not mean cleaving. Although not expressly stated by applicants, it appears applicants intend for the term

"removing the protein encoded by protein(Y) from the fusion protein" to be interpreted as meaning the protein encoded by protein(Y) is purified from a mixture of the protein encoded by protein(Y) and the fusion protein. However, it is noted that there is no indication in the specification and the claims that protein(Y) is separated from the fusion protein and it is unclear as to how one separates protein(Y) from the fusion protein without first cleaving the protein(Y) from the fusion protein. Clarification is requested.

[12] Claim(s) 1-2 and 7-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

Claim 1 (claims 2 and 7-20 dependent therefrom) is indefinite in the recitation of "hirudin derivative" as it is unclear as to how one of skill in the art distinguishes those derivatives of hirudin that are meant to be included within the scope of the term "hirudin derivative" and those proteins that are meant to be excluded. In other words, what characteristics distinguish a "hirudin derivative" that is included within the scope of the claim from those derivatives of hirudin that are not included within the scope of the claim? It is noted the specification discloses that "Hir" is a DNA or nucleic acid sequence coding for hirudin or a hirudin derivative that is "at least 40% homologous to a natural hirudin isoform." If the disclosure were limited to this definition, a skilled artisan could readily determine those hirudin derivatives that are meant to be included within the scope of the term. However, the specification further discloses that "[a hirudin] variant is derived from a natural hirudin isoform, but contains, for example, additional amino acids and/or amino acid deletions and/or amino acid exchanges compared with

the natural isoform" and that "[a] hirudin variant may contain alternating peptide segments of natural hirudin isoforms and new amino acids" (p. 10, top). In view of this additional disclosure, it is unclear as to the scope of proteins intended to be encompassed by the term "hirudin derivative." It is suggested that applicants clarify the meaning of "hirudin derivative."

Claim Rejections - 35 USC § 112, First Paragraph

[13] The written description rejection of claim(s) 1-2 and 7-20 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth at item [10] of the Office action mailed May 20, 2004 and for the reasons stated below.

RESPONSE TO ARGUMENT: Applicants assert it is a "remarkable" feature of the invention that fusion proteins having an N-terminal hirudin or hirudin derivative can be exported from yeasts in good yields. Applicants acknowledge the claimed genus of nucleic acids encompasses species that are widely variant in structure, asserting that as long as a nucleic acid has the structure as recited in claim 1, one of skill can select the proper components to encode the desired protein. Applicants' argument is not found persuasive.

In this case, the claims encompass a genus of nucleic acids comprising any promoter sequence (represented by Px), any signal or leader sequence (represented by Sx), any nucleic acid sequence encoding any hirudin (from any source – including hirudins yet to be isolated) or a hirudin derivative, which, as interpreted in accordance with MPEP 2111, is any protein (represented by Hir), and any untranslated expression-

enhancing nucleic acid (represented by T). It should be noted that protein(Y) is not considered by the examiner to be a critical or essential element of the claimed invention. As stated in a previous Office action, and undisputed by applicants, the specification discloses only three representative examples of the claimed genus of nucleic acids, disclosed in the specification at pp. 11-17 of the specification as Examples 1-3. These three representative species fail to describe all species of nucleic acids encompassed by the genus as described above. Given the lack of description of a representative number of nucleic acid sequences, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[14] The scope of enablement rejection of claim(s) 1-2 and 7-20 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth at item [11] of the Office action mailed May 20, 2004 and for the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue a skilled artisan would be able to identify nucleic acids having the formula recited in claim 1 that encode the desired protein. Applicants argue that only routine experimentation is necessary for a skilled artisan to make the full scope of claimed nucleic acids. Applicants' argument is not found persuasive.

As stated above, the claims are so broad as to encompass nucleic acids comprising any promoter sequence (represented by Px), any signal or leader sequence (represented by Sx), any nucleic acid sequence encoding any hirudin (from any source – including hirudins yet to be isolated) or a hirudin derivative, which, as interpreted in

accordance with MPEP 2111, is any protein (represented by Hir), and any untranslated expression-enhancing nucleic acid (represented by T). The scope of the claims is not commensurate with the disclosure of the specification, which provides only three working examples of the broad scope of claimed nucleic acids (see pp. 11-17 of the specification). With the exception of the disclosure of the hirudin variants at pp. 9-11 of the specification, the specification fails to provide guidance for altering any hirudin with an expectation that the encoded protein will have the characteristic of being "exported from yeasts with good yields similar to those of hirudin itself." For example, how is one of skill in the art to use those nucleic acids that encompass inactive hirudin variant fusion proteins that are not exported from yeast? It should be noted that applicants do not dispute the teachings of the reference of Branden et al., which teaches the high level of unpredictability in altering the amino acid sequence of a protein to obtain a desirable altered form thereof. In view of the broad scope of the claims, the lack of guidance and working examples, and the high level of unpredictability in the art, one is required to make and screen all nucleic acids as encompassed by the claims for those that have the desired utility of being exported from yeasts. Such experimentation is not, contrary to applicants' assertion, routine experimentation. As such, it is the examiner's position that undue experimentation is required to make and use the full scope of claimed nucleic acids.

Claim Rejections - 35 USC § 102

[15] The rejection of claims 1, 7-14, and 18-19 under 35 U.S.C. 102(b) as being anticipated by Dawson et al. is maintained for the reasons of record as set forth at item [12] of the Office action mailed May 20, 2004 and for the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue the reference of Dawson et al. does not anticipate the claims as the vector disclosed be Dawson et al. does not comprise a sequence that meets the formula of claim 1 in its sequence or its order of components. Applicants' argument is not found persuasive.

Applicants argue Dawson et al. teach mutagenesis of the alpha-factor pro-peptide sequence that links the hirudin encoding sequences to a Factor Xa cleavable sequence and that this teaching indicates that the vector of Dawson et al. does not satisfy the recited formula of claim 1. The examiner agrees with applicants' argument to the extent that the reference of Dawson et al. teaches mutagenesis of the alpha-factor pro-peptide sequence that links the hirudin encoding sequences to a Factor Xa cleavable sequence (see particularly columns 12-13). However, this teaching fails to obviate the rejection as the resulting (mutated) vector anticipates the claimed invention.

It appears that applicants have failed to recognize that the vector encoding the hirudin-Factor Xa cleavage site linker-hirudin fusion protein maintains an alpha-factor pro-peptide including a C-terminal linker of Ser-Leu-Asp-Lys-Arg coding sequence upstream of the first hirudin coding sequence. A careful reading of Dawson et al. indicates that Dawson et al. created a vector encoding an alpha-factor pro-peptide including a C-terminal linker of Ser-Leu-Asp-Lys-Arg fused to hirudin (columns 10-11). Dawson et al. then created a hirudin-hirudin (or hirudin-streptokinase) fusion protein by

ligating a nucleic acid fragment encoding alpha-factor pro-peptide including a C-terminal linker of Ser-Leu-Asp-Lys-Arg fused to hirudin (or streptokinase) downstream of the nucleic acid encoding an alpha-factor pro-peptide including a C-terminal linker of Ser-Leu-Asp-Lys-Arg fused to hirudin (or streptokinase) (see, *e.g.*, column 12). Thus, the mutagenesis was carried out on a vector comprising (in order): a galactose regulated promoter, nucleic acids encoding an alpha-factor pro-peptide including a C-terminal linker of Ser-Leu-Asp-Lys-Arg fused to hirudin fused to an alpha-factor pro-peptide including a C-terminal linker of Ser-Leu-Asp-Lys-Arg fused to hirudin (or streptokinase), and a yeast PGK terminator (See Example 1, columns 11-13 and Examples 8-9, columns 25-27). The mutagenesis was conducted to mutate the second alpha-factor pro-peptide (between the two hirudin or hirudin-streptokinase moieties) to a Factor Xa cleavable site. The resulting vector comprises (in order) a galactose regulated promoter, nucleic acids encoding an alpha-factor pro-peptide including a C-terminal linker of Ser-Leu-Asp-Lys-Arg fused to hirudin fused to a Factor Xa cleavable linker fused to hirudin (or streptokinase), and a yeast PGK terminator. As previously stated, Dawson et al. teach expression of the hirudin-hirudin or hirudin-streptokinase fusion proteins by culturing Saccharomyces cerevisiae transformed with the expression vector, followed by isolation of the fusion protein (Example 2, columns 13-14 and Example 15, column 32). This anticipates claims 1, 7-14, and 18-19 as written.

Claim Rejections - 35 USC § 103

[16] The rejection of claims 15-16 under 35 U.S.C. 103(a) as being unpatentable over Dawson et al. in view of Badziong et al. and the rejection of claim 17 under 35 U.S.C. 103(a) as being unpatentable over Dawson et al. in view of Bischoff et al. are maintained for the reasons set forth at items [13] and [14], respectively, of the Office action mailed May 20, 2004 and the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue that, because Dawson et al. does not disclose the claimed nucleic acid, by combining the teachings of Dawson et al. with Badziong et al. or Bischoff et al., one of ordinary skill in the art would not arrive at the claimed invention. Applicants' argument is not found persuasive.

Contrary to applicants' assertion, Dawson et al. anticipate the invention of claims 1, 7-14, and 18-19, at least for the reasons stated above. Moreover, Dawson et al., in combination with the reference of Badziong et al. or Bischoff et al., would have rendered obvious the invention of claims 15-16 or 17, respectively, at the time of the invention.

Claim Rejections – Double Patenting

[17] The provisional double patenting rejection of claim 1 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of US non-provisional application 10/076,634 and claim 1 of US non-provisional application 10/076,631 is maintained for the reasons of record as set forth at items [15] and [16], respectively, of the Office action mailed May 20, 2004 and for the reasons stated below.

RESPONSE TO ARGUMENT: Although applicants disagree with the rejection, they present no line of reasoning that would obviate the provisional rejections. In view of

applicants' failure to overcome the provisional rejections, the instant rejections are maintained for the reasons of record.

Conclusion

[18] Status of the claims:

- Claims 1-20 are pending.
- Claims 3-6 are withdrawn from consideration.
- Claims 1-2 and 7-20 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Primary Examiner
11-24-04